PATENT SPECIFICATION

NO DRAWINGS

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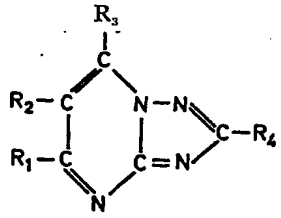
COMPLETE SPECIFICATION

s-Triazolo(1,5-a) pyrimidines Substituted in the 7-Position by a Basic Group

We, VEB. DEUTSCHES HYDRIERWERK RODLEBEN, of 453 Rosslau/Elbe, Eastern Germany, a Corporation organised and existing under the laws of Eastern Germany, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to s-triazolo-(1,5-a) pyrimidines substituted in the 7-position by a basic group, and their acid addition salts, which compounds have the general formula I.



(I)

wherein:—

each of R_1 and R_4 is a hydrogen or halogen atom or an alkyl group (chain length C_1 to C_3), an alkoxyalkyl group, or an aralkyl or aryl group which may be substituted in the nucleus.

R_2 is a hydrogen or halogen atom or a lower alkyl (up to 4 C atoms), alkenyl, aralkyl or aryl group.

R_3 is a free amino group, or an amino group substituted by the same or different groups in which case the groups can be alkyl, cyclo-alkyl, alkenyl, hydroxy-alkyl, alkyl-amino-alkyl or alkoxy groups, or possibly substituted aryl or aralkyl groups or heterocyclic groups or R_3 is a hydrazino or guanidino group or R_3 is a tertiary cyclic amino group or a basically substituted, straight or branched chain C_2—C_4 alkoxy group the basic group being any one of the aforementioned amino, substituted-amino, guanidino, hydrazino or cyclic amino group.

Surprisingly, it has been found that basically substituted s-triazolo(1,5-a) pyrimidines, when tested on animals had a coronary vasodilative effect which was not previously known in connection with this class of compounds and which was superior to known compounds, this having been proved by comparative tests. The tests were carried out on isolated hearts of mammals by the Langendorff method (Pflügers Archiv 61, 219 (1895), as modified by Ryser and Wilbrandt (Arch.int.pharmacodyn. XCVI 131(1953)). It was found here that, inter alia, the compounds 2,5-dimethyl-7 - furfurylamino - and 5 - methyl - 7 - dimethylamino - and 5 - methyl - 7 - benzylamino - s - triazolo (1,5 - a) pyrimidine had 10—20 times the coronary vasodilative effect of euphyllin and theocor. In the tests on the entire animal, measuring the throughput in the coronary vessels with a Nycotron flow meter applied to the unopened coronary vessel, a dose of 1 mg/kg resulted in an initial increase of the throughput to 2—3 times the normal rate for a period of 4—5 minutes, followed by a lasting increase of the coronary throughput to 1.2—1.5 times the

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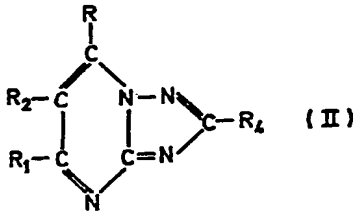
normal rate for 200 minutes. Comparable measurements with prenylamine show far less striking effects.

These compounds are therefore to be used for the therapy of afflictions of coronary vessels.

According to this invention there are provided methods for the production of s-triazolo (1,5-a) pyrimidines of the formula I.

The compounds of formula I in which R_3 is an amino, a substituted amino, a tertiary cyclic amino, a hyrazino or a guanidino group are prepared by reacting, s-triazolo (1,5-a) pyrimidines of the formula II



(II)

where R is halogen or a mercapto, an alkylmercapto or alkoxyl group and R_1, R_2 and R_4 are as set out in Formula I, with the corresponding compounds of the general formula R_3H where R_3 is as set forth above.

Preferably the reaction between compounds of the Formula (II) in which R is halogen and compounds of the formula R_3H is carried out in a solvent such as water or water/alcohol mixtures at a temperature between 0°C and the boiling point of the solvent, the resulting bases being converted into salts by treatment with acids.

The solvent may be in addition to water, and mixtures of water and alcohols, benzol, dioxane or chloroform. The use of water as a solvent enables the reaction to be carried out particularly simply and neatly when the desired basically substituted compounds are to be produced from the halogen compound without first isolating the latter. To neutralise the halogen hydracid released in the reaction, amines, e.g. triethylamine, or alkali metal carbonates are required in excess. The reaction products are worked up in the usual manner, the final products being separated from the halogen compounds formed and purified by recrystallization, extraction or distillation.

The synthesis of the basically substituted s-triazolo (1,5-a)pyrimidines can also be carrned out by reacting compounds of the general formula (II), in which R is a mercapto, alkylmercapto or alkoxy group with an excess of compounds having the general formula R_3H, at the boiling point of the solvent, which may be ethanol or dioxane. This process is accompanied by the escape of hydrogen sulphide or an alkyl mercaptan or separation of an alcohol, and the final product, which is purified as above, remains in solution.

The basically-substituted alkoxy compounds with a normal or branched alkyl chain of 2—4 carbon atoms are produced by reacting compounds of the general formula (II), in which R is chlorine or bromine, with the sodium compounds of appropriate basically-substituted alkanols. The solvent used consists of the basically-substituted alkanol used in excess. The resulting compounds are purified as previously described.

The substituted 7-chloro- or 7-bromo-s-triazolo-(1,5a) pyrimidines used as starting substances may be produced by reaction of the corresponding 7-hydroxy compounds with a phosphorus halide in the presence of N,N-dimethyl aniline or N,N-dimethyl formamide. The substituted 7-mercapto-s-triazolo-(1,5a)pyrimidines are obtained, in a manner already known in itself, by the reaction of the halogen compound with thiourea and subsequent alkaline hydrolysis or by thiolation of the 7-hydroxy compounds with phosphorus pentasulphide. The subsequent reaction with alkylation agents results in the 7-alkylmercapto-s-triazolo(1,5a) pynimidines, while the 7-alkoxy compounds are produced from the halogen compounds by means of alkali alcoholates.

The required 7-hydroxy-s-triazolo(1,5a) pyrimidines are obtained by the condensation of a possibly substituted 5-amino-1,2,4-triazole with a possibly substituted 1,3-dicarbonyl compound.

The compounds obtained can be converted into their salts by treatment with acids.

Examples of the process of the invention will be given.

Example 1

5.1 g of 7-chloro-s-triazolo(1,5a) pyrimidine were kept at moderate reflux in 50 cc of water with 9.6 g of diethylamine for 5 hours. The reaction solution was evaporated under vacuum and the residue extracted with petroleum ether. After re-crystallization from n-heptane, 3 g of colourless crystals of 7-diethylamino-s-triazolo(1,5a) pyrimidine with a melting point of 68°C were obtained.

Example 2

4.6 g of 7-chloro-s-triazolo(1,5a) pyrimidine were refluxed in 50 cc of water with 6.4 g of benzylamine for 5 hours, the process being accompanied by stirring. The reaction solution was then cooled, the crystallized product removed by suction and the residue recrystallized from ethanol. The resulting 7-benzylamino-s-triazolo(1,5a) pyrimidine (5.2 g) had a melting point of 216—217°C.

Example 3

8.8 g of 2-ethyl-5-methyl-7-chloro-s-tri-

azolo (1,5a) pyrimidine were kept in 50 cc of water with 7.5 g of diethylamine for 2.5 hours, while stirring and with moderate refluxing. The reaction product was concentrated until dry and acetone added to the residue. The hydrochloride remained in an undissolved state. After evaporation of the acetone, the remaining liquid was distilled and the distillate re-crystallized from ether. This yielded 5.9 g of colourless crystals of 2-ethyl-5 - methyl - 7 - diethylamino - s - triazolo - (1,5-a) pyrimidine, which had a melting point of 61—63°C.

EXAMPLE 4

2.5 g of furfurylamine were added to 50 cc of ethanol in order to dissolve 4 g of 5-methyl - 6,7 - dichloro - s - triazolo(1,5 - a) pyrimidine. The mixture was refluxed in a steam bath for 3 hours, after which it was concentrated under a vacuum until dry and the residue recrystallized from water/dioxane. This process yielded 4.5 g of 5-methyl-6-chloro - 7 - furfurylamino - s - triazolo(1,5 - a) pyrimidine which had a melting point of 163°C.

EXAMPLE 5

4.6 g of 5 - methyl - 6 - bromo - 7 - chloro-s-triazolo (1,5-a) pyrimidine were refluxed for 5 hours in 20 g of diethylamine with stirring. The excess diethylamine was then distilled off, water was added, and the residue removed by suction. The resulting 5-methyl - 6 - bromo - 7 - diethylamino - s - triazolo (1,5-a) pyrimidine (3.8 g) had a melting point of 84—86°C.

EXAMPLE 6

1.2 g of metallic sodium were dissolved in 60 g of diethylamino-ethanol. 12.5 g of 5-methyl - 7 - chloro - s - triazolo(1,5 - a) - pyrimidine were then added, and the mixture heated for 3 hours in a bath at a temperature of 130—140°C. The excess diethylamino-ethanol was distilled off under vacuum, and the residue boiled out with n-heptane. The yield was 8.5 g. The 5-methyl-7-(β-diethylamino - ethoxy) - s - triazolo(1,5 - a) pyrimidine had a melting point of 113—114° C.

EXAMPLE 7

7.6 g of 2 - isopropyl - 5 - methyl - 7 - chloro-s-triazolo(1,5-a) pyrimidine and 6.5 g of piperidine were refluxed with 50 cc of water for 2.5 hours. The mixture was then concentrated under vacuum until dry, and recrystallised with n-heptane or distilled under high vacuum (boiling point $_{0.6}$ of 200—202° C). This process yielded 3.5 g of 2-isopropyl-5 - methyl - 7 - piperidino - s - triazolo (1,5-a) pyrimidine, with a melting point of 73—75°C.

EXAMPLE 8

8.4 g of 5 - methyl - 7 - chloro - s - triazolo (1,5-a) pyrimidine were dissolved in 75 cc of ethanol; 5.5 g of triethylamine and 4.5 of n-amylamine were added, and the mixture refluxed for 5 hours in a steam bath. The reaction solution was concentrated under vacuum until dry and extracted with n-heptane. Recrystallization from n-heptane yielded 8 g of 5 - methyl - 7 - n - amyl - amino-s-triazolo(1,5-a) pyrimidine, with a melting point of 111—112°C.

EXAMPLE 9

5 g of 2 - (3',4',5' - trimethoxy - phenyl) - 5 - methyl - 7 - chloro - s - triazolo (1,5 - a) pyrimidine were refluxed in 75 cc of butanol with 3.5 g of piperidine for 10 hours while stirring. The excess n-butanol was distilled off under vacuum and the residue removed by suction and recrystallised from isopropanol. This process yielded 2.3 g of the 2-(3',4',5'-trimethoxy - phenyl) - 5 - methyl - 7 - piperidino - s - triazolo - 1,5 - a) pyrimidine, with a melting point of 186—187°C.

EXAMPLE 10

5.7 g of 5 - phenyl - 7 - chloro - s -triazolo (1,5-a) pyrimidine and 5.3 g of diethanolamine were introduced into 50 cc of butanol and the mixture was refluxed for 5 hours. The solvent was then distilled off under vacuum. The residue was dissolved in dilute acetic acid and filtered. The filtrate was adjusted to pH5 with soda solution. The resulting oil became solid after a period of time. Recrystallization from water yielded 6.2 g of the 5 - phenyl - 7 - diethanolamino - s - triazolo (1,5-a) pyrimidine, in the form of colourless crystals, with a melting point of 163—165°C.

EXAMPLE 11

3.7 g of 2 - phenyl - 5 - methyl - 7 - chloro-s-triazolo (1,5-a) pyrimidine and 2.7 g of piperidine were introduced into 50 cc of butanol. After 5 hours stirring and refluxing, the excess n-butanol was distilled off and the residue extracted with benzine. The resulting 2 - phenyl - 5 - methyl - 7 - piperidine - s - triazolo (1,5-a) pyrimidine (6g) had a melting point of 174—175°C.

EXAMPLE 12

6.4 g of o-chloro-aniline and 4.3 g of 5-methyl - 7 - chloro - s - triazolo (1,5 - a) pyrimidine were carefully heated in a water bath. This resulted in a vigorous reaction, and the reaction mixture became liquid. The resulting melt was extracted with boiling water and recrystallized from isopropanol/water. The yield was 4.5 g of 5-methyl-7-(o-chloro - anilino) - s - triazolo (1,5 - a) pyrim - idine, with a melting point of 177°C.

EXAMPLE 13

4.3 g of 5 - methyl - 7 - chloro - s - tri - azolo (1,5-a) pyrimidine and 4.2 g of p-

amino-benzoic acid ethyl ester were refluxed for 5 hours in 50 cc of ethanol. The ethanol was then distilled off and water added to the residue. After removal by suction and recrystallization from toluene, this proces yielded 7 - (p - carbethoxy - anilino) - 5 - methyl - s-triazolo (1,5-a)pyrimidine, with a melting point of 185°C.

EXAMPLE 14

6.5 g of N,N-diethyl-propylene diamine and 4.6 g of 5 - methyl - 6 - bromo - 1 - chloro-s-triazolo (1,5-a) pyrimidine were refluxed in 50 cc of ethanol for 5 hours. The mixture was then concentrated under vacuum and water added and the residue recrystallized from water ethanol. The N,N-diethyl-N' - [5 - methyl - 6 - bromo - s - triazolo (1,5-a) pyrimidinyl - (7)] - propylene diamine had a melting point of 120°C.

EXAMPLE 15

3.6 g of 5 - methyl - 7 - methyl - mer - capto-s-triazolo (1,5-a) pyrimidine, 4.2 g of benzylamine and 50 cc of iso-propanol were refluxed until the formation of methyl-mercaptan ceased. The mixture was allowed to cool, removed by suction and re-crystallized from water/iso-propanol. This process yielded 2.5 g of the 5-methyl-7-benzylamino-s-triazolo (1,5-a) pyrimidine, which had a melting point of 162—163°C.

EXAMPLE 16

2.7 g of 2,5-dimethyl-7-ethoxy-s-triazolo-(1,5-a) pyrimidine, 6 g of furfurylamine and 10 cc of isopropanol were left to stand for 2 days at room temperature. The resulting precipitate was removed by suction and recrystallized from water/isopropanol. This process yielded 2.5 g of the 2,5-dimethyl-7-furfuryl - amino - s - triazolo (1,5 - a) pyrimidine. Melting point: 189:190°C.

EXAMPLE 17

3.4 g of 2,5-dimethyl-7-ethoxy-s-triazolo (1,5-a) pyrimidine, 12 g of benzylamine and 10 cc of isopropanol were refluxed for 3 hours. The iso-propanol was distilled off. Recrystallization from water/isopropanol resulted in 3 g of 2,5-dimethyl-7-benzylamino-s-triazolo (1,5-a) pyrimidine, which had a melting point of 162—163°C.

EXAMPLE 18

2.7 g of 2,5-dimethyl-7-ethoxy-s-triazolo (1,5-a) pyrimidine, 5 g of piperidine and 10 cc of isopropanol were left to stand for 2 days at room temperature. The reaction solution was then concentrated. The residue was suspended in a smal quantity of water, dissolved with the addition of hydrochloric acid and filtered. The base was precipitated by 25% strength potash lye in the form of an oil which slowly solidified. Recrystallization from n-heptane yielded 2.7 g of the 2,5-dimethyl - 7 - piperidino - s - triazolo (1,5-a) pyrimidine which had a melting point of 93—94°C.

EXAMPLE 19

8.4 g of 5-methyl-7-chloro-s-triazolo (1,5-a) pyramidine were suspended in 30 cc of water and 7.3 g of diethyl amine added. After two hours heating with stirring, the mixture was concentrated under vacuum. The residue was recrystallized from n-heptane. This process yielded 8.1 g of the 5-methyl-7-diethylamino-s-triazolo(1,5-a) pyrimidine having a melting point of 103—104°C. The hydrochloride produced in the usual manner had a melting point of 212°C.

EXAMPLE 20

8.4 g of 2,5-dimethyl-7-chloro-s-triazolo (1,5-a) pyrimidine was suspended in 25 cc of water, to which was added dropwise, 7.3 g of isobutylamine. The mixture was then heated for two hours and concentrated under vacuum. The residue was re-crystallized from benzene. The 2,5 - dimethyl - 7 - isobutyl - amino-s-triazolo (1,5-a) pyrimidine (5 g) had a melting point of 97—98°C. The addition of ethereal HCl to the compounds dissolved in acetone resulted in the hydrochloride, with a melting point of 148°C (butanol/ether).

WHAT WE CLAIM IS:—

1. Process for the production of s-triazolo (1,5-a) pyrimidines substituted in the 7-position by a basic group and which have the general Formula (I) as herein set forth, in which the basic group (R_3) is either an amino group, a substituted amino group, a tertiary cyclic amino group a hydrazino group or a guanidino group, which consists in reacting s-triazolo (1,5-a) pyrimidines of the formula II as set forth, where R is a halogen atom or a mercapto or alkylmercapto group and R_1, R_2 and R_4 as set out in Formula I with the corresponding compounds of the general Formula R_3H in which R_3 is as defined above.

2. Process for the production of s-triazolo (1,5-a) pyrimidines substituted in the 7-position by a basic group and which have the general Formula (I) as herein set forth and in which the basic group (R_3) is a basically-substituted alkoxy group with a normal or branched alkyl chain of 2—4 carbon atoms, which consists in reacting s-triazolo (1,5-a) pyrimidines of the Formula II as herein set forth in which R is a halogen atom and R_1, R_2 and R_4 are as set forth in Formula I with the corresponding sodium alcoholates of the general formula R_3Na in which R_3 is as defined above.

3. Process in accordance with Claim 1 or 2, wherein the reaction is carried out in the presence of acid binding agents and/or solvents.

4. Process in accordance with Claim 3,

wherein the acid binding agents are amines or alkali metal carbonates.

5. Process in accordance with Claim 1, wherein the reaction between compounds of the formula (II) in which R is halogen and compounds of the formula R_3H, is carried out in water or water/alcohol mixtures at a temperature between 0°C and the boiling point of the solvent, the resulting bases being converted into salts by treatment with acids.

6. Process in accordance with Claim 1, wherein the reaction between compounds of the formula (II) in which R is a mercapto, alkylmercapto or alkoxy group and compounds of the formula R_3H, is carried out at the boiling point of the solvent which is ethanol or dioxane.

7. Process for the production of s-triazolo (1,5-a) pyrimidines in accordance with Claims 1 and 2, substantially as herein described.

8. Compounds of the general formula (I) when produced by the process of any one of the preceding Claims 4 to 7.

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